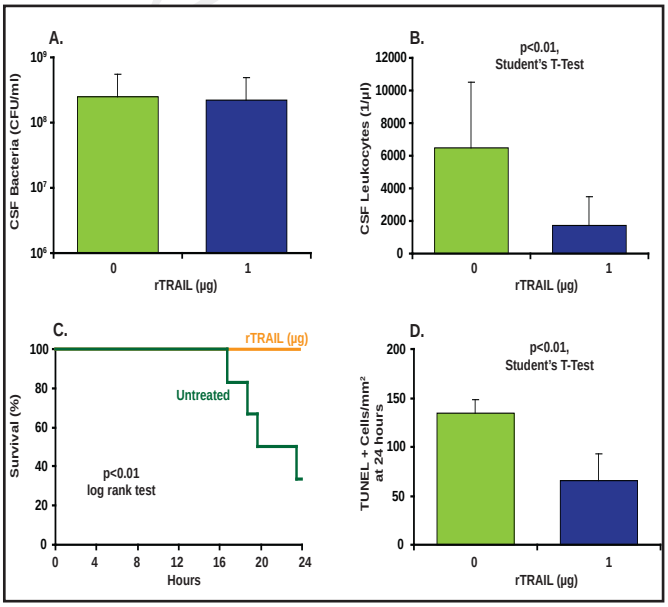
The Role of Adjunctive Steroids in the Treatment of Bacterial Meningitis

Written by Noelle Lake, MD

Steroids have an important place in the treatment of bacterial meningitis (BM), according to W. Michael Scheld, MD, University of Virginia, Charlottesville, Virginia, USA. Dr. Scheld was unable to attend this year's ICAAC, but graciously agreed to share highlights from that talk for the benefit of *MD Conference Express* readers.

The rationale for employing anti-inflammatory medication in the treatment of BM is based upon the observation that hyperactive central nervous system (CNS) immune responses underlie brain swelling and neuronal loss and likely contribute to morbidity and mortality. In animals, steroids have been shown to reduce CNS inflammation, intracranial pressure, and neuronal loss. In addition, new investigational anti-inflammatory agents, such as recombinant tumor necrosis factor-related apoptosis-inducing ligand (rTRAIL), significantly decrease cerebrospinal fluid leukocytes and apoptosis in mouse models of pneumococcal meningitis and significantly improve survival (Figure 1) [Hoffmann O et al. *J Clin Invest* 2007].

Figure 1. Effects of Treatment with rTRAIL in Meningitis Induced By Live *pneumococci* in Mice.



(A) At 24 hours after infection, CSF bacterial load in untreated and rTRAIL-treated wild-type mice did not differ. (B) CSF leukocyte concentration was significantly lower in rTRAIL-treated mice than in controls. **p<0.01, Student's t-test. (C) Mortality was higher in untreated versus rTRAIL-treated mice. **p<0.01, log rank test. (D) Apoptosis was reduced by treatment with rTRAIL. **p<0.01, Student's t-test.

After review of the clinical literature over the past decade, Dr. Scheld believes that intravenous dexamethasone for the first 2 to 4 days in the treatment of community-acquired BM is indicatedin all ages in developed nations. De Gans et al. demonstrated an overall reduced risk for unfavorable outcomes and mortality in adults (RR=0.59; 95% CI, 0.37 to 0.94; p=0.03; and RR=0.48; 95% CI, 0.24 to 0.96; p=0.04, respectively) with dexamethasone [*New Engl J Med* 2002]. Data from the Netherlands reveal that national implementation of adjunctive dexamethasone in patients with *S. pneumoniae* BM has significantly reduced unfavorable outcomes, hearing loss, and mortality [Brouwer MC et al. *Neurology* 2010].

In contrast, steroids are not recommended where resources are limited and in populations with high HIV-positivity rates. A Vietnamese study showed a benefit to dexamethasone use only among patients with a proven microbiological diagnosis of BM but not among those with a probable diagnosis [Nguyen TH et al. *New Engl J Med* 2007]. A study in Malawi among patients with high rates of HIV infection showed no benefit to using steroids in the treatment of BM [Scarborough M et al. *New Engl J Med* 2007]. Further, a 2010 meta-analysis that examined the issue showed that benefits of reduced hearing loss and neurologic sequelae, but not overall mortality among patients with BM who were treated with adjunctive steroids were observed in developed nations only [Brouwer MC et al. *Cochrane Rev* 2010].

Other potential strategies for improving BM outcomes include selection of highly bactericidal, non lytic antibacterials such as rifampin, which has been shown to reduce β-lactam-induced cytotoxicity in animals [Spreer A et al. *Crit Care Med* 2009], and daptomycin plus ceftriaxone, which has been associated with reduced neuronal injury and hearing loss [Grandgirad et al. ECCMID 2009]. In addition, prompt initiation of antibacterial therapy has been shown to reduce mortality [Proulx N et al. *Q J Med* 2005; Auburtin M et al. *Crit Care Med* 2006] and remains a central tenant of proper treatment.

Human and Animal Viruses Share "One World" and Emerging Zoonotic Infections Continue to Threaten

Written by Noelle Lake, MD

While infectious diseases are no longer a major cause of mortality in developed countries, new viral infections continue to emerge due to our globalizing and changing

world, as well as improved detection methods. In the 2011 ICAAC lecture, Albert Osterhaus, PhD, Erasmus Medical Center, Rotterdam, The Netherlands, made the point that, "the human species is just another animal species that really belongs to an ecosystem." Public health, animal health, the food supply, world economies, and biodiversity all depend on anticipating and controlling new viral outbreaks [Kuiken T et al. *Science* 2005].

Contributing factors for viral crossover from animals include animal contact, human behaviors, urbanization, air travel, wars, poverty, medical practices, and viral adaptation. The ongoing AIDS pandemic is a powerful example of the devastation that can arise from the passage of animal viral strains to humans, as HIV-1 and HIV-2 originated in chimpanzees sooty mangabeys, respectively.

Prof. Osterhaus cautioned that vaccine success comes with potential risks. The eradication of smallpox is perhaps the twentieth century's major medical achievement, but now we are seeing a rise in other Orthopoxviruses in humans, including cowpox and monkeypox, which is fatal in up to 5% of cases [Stittelaar K et al. *Nature* 2006; Pelkonen PM et al. *Emerg Infect Dis* 2003]. Notably, this year marks the second successful global eradication of a mammalian virus, Rinderpest, a morbillivirus viral disease in cattle that is closely related to measles. Other morbilliviruses, however, continue to cause deadly outbreaks among animals year after year, such that even as strides are made toward the global eradication of measles, the possibility of emergence of a human morbillivirus from the animal world is strong and discontinuation of measles vaccine may not be recommended, even if measles is eradicated.

Prof. Osterhaus emphasized that the discovery of new viruses requires a team approach that utilizes clinicians, pathologists, epidemiologists, and laboratory evaluation with both classical virological and novel molecular techniques. The discovery of the severe acute respiratory syndrome (SARS) coronavirus involved identifying a new clinical syndrome, culturing and sequencing the SARS virus, creating an animal model of disease, and then testing antivirals in infected animals. Epidemiologists traced the mammalian source to a similar virus in carnivores in live animal markets in Hong Kong and China, which likely received the virus from bats. Since bats constitute 60% of all mammals on the globe, the virus can be spread quite easily.

Another virus that required fast, coordinated action was West Nile virus (WNV) which was introduced in the United States (US) in 1999, likely via air transport of infected mosquitoes, and spread rapidly across the US via mosquitoes as vectors and birds as intermediate hosts. The first serodetection of WNV in Europe was in 1958 in Albania. With recent cases and virus isolation on several European borders, Prof. Osterhaus and his team are following WNV closely.

Other potentially threatening emerging viruses include human metapneumovirus (hMPV), chikungunya virus, Hendra and Nipah viruses, and avian flu. hMPV crossed the species barrier from birds over 200 years ago and is currently responsible for 10% of the severe respiratory infections in young children. Chikungunya causes a severe flu-like illness and has the potential to spread widely within southeastern US, which shares the same mosquito vector with the northern Italian town where it emerged in 2007. Transmitted from fruit bats, outbreaks of Hendra virus in horses in Australia and the related Nipah virus in pigs in Malaysia caused hundreds of deaths among farmers and handlers in the late 1990s and continues to cause disease throughout Bangladesh [Luby SP et al. *Emerg Infect Dis* 2009].

Avian flu represents a crossover from birds (or sometimes pigs) to humans, and has only occurred in sporadic, isolated cases to date (Table 1). Although avian flu is highly pathogenic and frequently fatal, a pandemic would require that the virus develop better human-to-human transmissibility. Unfortunately, mutant H5N1 strains that have been created in the laboratory have been shown to be transmissible between ferrets, an indication that human-to-human spread could evolve [Munster VJ et al. *Science* 2009].

Prof. Osterhaus concluded by urging international coordination around outbreaks, collaboration between public and private sectors, and use of all available technology for effective control of emerging infections.

Table 1. Recent Zoonotic Transmissions.

Subtype	Country	Year	No. Cases	No. Deaths
H7N7	United Kingdom	1996	1	0
H5N1	Hong Kong	1997	18	6
H9N2	Southeast Asia	1999	>2	0
H5N1	Hong Kong	2003	2?	1
H7N7	Netherlands	2003	89	1
H7N2	USA	2003	1	0
H7N3	Canada	2004	2	0
H5N1	Southeast Asia/ Middle East/Europe/ West Africa	2003-11	>550	>320*

*=CFR~60%